Discussion

From our previous work we knew that the epidemic of tonsillitis we described was not controlled by the treatment of cases and carriers alone and that full penicillin prophylaxis to all boys on entry was essential. This regimen entailed giving penicillin four times a day; this was difficult to administer and was stopped in 1978, when the epidemic seemed to be under control. Though these measures appeared to be effective, we were unable to claim with certainty that the improvement was anything more than fortuitous. A further epidemic began within eight weeks of stopping the prophylaxis (March 1978), which made it more likely that the control we had reported had resulted from penicillin prophylaxis.

This new epidemic presented an opportunity to try to determine the minimum amount of prophylactic penicillin required for control. From our results 0·5 g oral phenoxymethylpenicillin given daily to all boys for 10 days after entry seemed effective; when administered at breakfast and before dispersal to their various activities this was not unduly disruptive.

Four cases of rheumatic fever occurred in our first survey and there were two further cases during this epidemic. Since the incidence of rheumatic fever in the United Kingdom is now believed to be very low, these attacks highlight the need to control epidemics of tonsillitis in closed communities.

Once again we found a sluggish response to prophylaxis. From our previous experience, perhaps we should have foreseen that it would take time to bring the epidemic under control. We do not know whether we could have achieved a quicker response by treating all boys who were in the centre at the height of the epidemic with oral penicillin, but this would seem likely.

There may well be a difference between controlling epidemics in closed communities, such as detention centres, which have a changing population, and semi-closed communities, such as boarding schools, which have a more fixed population. Gastanaduy *et al*[2] recently reported an epidemic in a semi-closed community of 300 people that was brought under control in three or four months by the administration of intramuscular penicillin or oral antibiotics (phenoxymethylpenicillin or erythromycin) to cases and carriers.

We have already suggested that adolescent boys may be particularly prone to *Streptococcus pyogenes* infections. Bringing together boys of this age group into closed communities will compound the problem, especially if the population is always changing. We do not have figures from other detention centres, but we are told that sore throats are very common. We suspect that our experience at Kirklevington is not unique and in the relatively socially deprived group of boys in detention centres the risk of developing rheumatic fever may well be higher than in the general population.

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SHORT REPORTS

Do patients receiving regular haemodialysis need folic acid supplements?

Patients receiving regular haemodialysis often receive folic acid supplements because foods rich in this vitamin often need to be restricted and loss across the dialysis membrane is likely to occur because of its low molecular weight and only moderate protein binding.[1 2] We have shown that the loss of folic acid during dialysis is equivalent to a daily loss only slightly greater than the urinary loss in normal subjects,[3] and in a retrospective study we found no evidence of folate deficiency in 72 patients who had received haemodialysis for a mean of 49 months.[3] We now report the results of a double-blind placebo-controlled crossover study to investigate the change in haemoglobin concentration and mean corpuscular volume during six months of treatment with folic acid.

Patients, methods, and results

Twenty-nine patients (16 men, 13 women) aged 18-59 (mean 42) who had received regular haemodialysis for nine to 143 (mean 69) months, entered the study. All were taking iron supplements (Ferrogradumet) orally once daily and none had received folic acid, cobalt chloride, androgens, or a blood transfusion within the preceding six months. The patients were divided into two groups of similar size matched for age, sex, and haemoglobin concentration. Group 1 received folic acid 5 mg daily and group 2 a matching placebo. After six months the groups crossed over, group 1 receiving placebo and group 2 folic acid for a further six months. Haemoglobin concentration and mean corpuscular volume were measured monthly by using a Coulter counter. Serum and red cell folate concentrations were measured at entry and at six and 12 months using a competitive binding assay (Becton Dickinson folate radioassay kit). The patients were seen monthly and completed a questionnaire regarding symptoms and blood loss, grading them as "none," "slight," or "troublesome" (scored 0, 1, or 2 in the analysis).

The significance of changes in haematological variables was measured using non-parametric regression analysis.

Six patients failed to complete the 12 months' trial. Two were withdrawn for transfusion, one after five months' treatment with placebo and the other after six months' treatment with folic acid. Four further patients were withdrawn while taking placebo; one because of sleeplessness, one headache and nausea, one penile irritation, and one worsening psoriasis. Red cell and serum folate concentrations were normal in all patients at entry. They rose significantly during treatment with folic acid and not during placebo periods, confirming compliance with trial medication. The order in which the treatments were given did not appear to contribute to the treatment effect. Blood loss reported during the treatment periods was similar. The mean haemoglobin concentration on entry was 8·0 g/dl. During treatment with folic acid there was a mean fall of 0·38 g/dl and a mean rise during placebo treatment of 0·25 g/dl. This difference is not significant ($p > 0·05$). The 95% confidence limits for the difference between folic acid and placebo are $-1·49$ and 0·23, corresponding to a fall of 1·49 g/dl on folate to a fall of 0·23 g/dl on placebo. Changes in mean corpuscular volume did not differ significantly. Symptoms of nausea, headache, vivid dreams, agitation, and irritability were slightly more common during treatment with folic acid, and anorexia, blurred vision, and sleep disturbance more common during treatment with placebo. None of these differences approached significance. The results were essentially unaltered by including data from the six patients withdrawn from the trial.

Comment

This study has shown no benefit from six months' treatment with folic acid and indeed a slight fall in haemoglobin concentration occurred during treatment with folic acid. In addition, there was a weak association with nausea, headache, vivid dreams, agitation, and irritability, symptoms that have been ascribed to folic acid previously.[4] We therefore see no justification for the use of folic acid supplements for adequately nourished patients receiving regular haemodialysis.

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Thyrotoxicosis presenting as fracture of femoral neck

Thyrotoxicosis, though an established cause of osteoporosis, rarely presents with bone fracture. We report two cases of thyrotoxicosis presenting as fracture of the femoral neck without other clinical features. All methods have been described previously.[1 2]

Case reports

CASE 1

A 64-year-old woman presented with a subcapital fracture of the right femur after minimal trauma. She had been noted to have a goitre when aged 27 but had never had symptoms of thyrotoxicosis. On examination a goitre was palpable but there were no signs of thyrotoxicosis.

Plasma calcium, phosphate, and creatinine concentrations and alkaline phosphatase activity were normal, but there was evidence of increased bone resorption with a high fasting urine hydroxyproline:creatinine ratio (0·06 molar units; normal $<0·02$). There was malabsorption of calcium (radiocalcium absorption 0·20 fraction of dose/hour; normal 0·3-1·4); low plasma 1,25-dihydroxy vitamin D concentration (64·2 pmol/l (25·7 pg/ml); normal 75-165 pmol/l (30-66 pg/ml)); and normal plasma 25-hydroxy vitamin D concentration (66·5 nmol/l (26·6 ng/ml); normal 42·5-215 nmol/l (17-86 ng/ml)) and plasma parathyroid hormone concentration (345 pg/ml; normal 53-450). There was radiological evidence of cortical osteoporosis (metacarpal cortical area:total area 0·51; mean$\pm$SD for age-related normal women 0·75$\pm$0·06) and histological evidence of trabecular osteoporosis (iliac crest bone volume 9%; normal >15%). Thyrotoxicosis was shown by a raised thyroxine concentration (157 nmol/l (12·2 μg/100 ml); normal 60-140 nmol/l (4·7-10·9 μg/100 ml)); triiodothyronine concentration (5·0 nmol/l (3·3 ng/ml); normal 1·6-3·0 nmol/l (1·0-2·0 ng/ml)); and free thyroxine index (4·6; normal 1·3-3·2). She was treated with carbimazole and was biochemically euthyroid after three weeks. Bone resorption as assessed by the urinary hydroxyproline:creatinine ratio took much longer to return to normal (figure).

CASE 2

A 66-year-old woman presented with a fracture of the left femur, having fractured the right femur a year earlier. The fracture was considered to have been due to osteomalacia and when seen by us she had already received four weekly doses of 50 000 units vitamin D. There were no symptoms or signs of thyrotoxicosis.

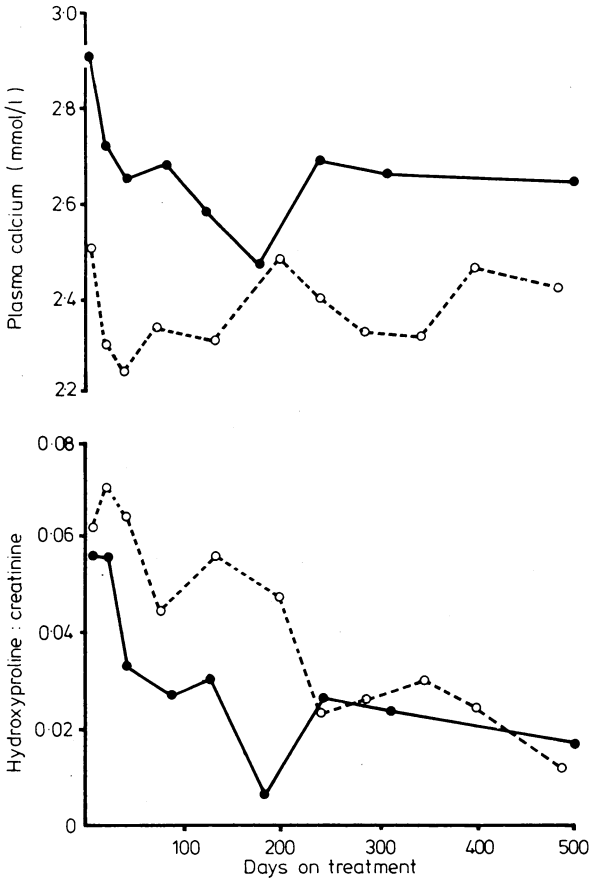
Plasma calcium concentration was raised (2·90 mmol/l (11·6 mg/100 ml); normal 2·25-2·60 mmol/l (9·0-10·4 mg/100 ml)), but plasma phosphate and creatinine concentrations were normal. Alkaline phosphatase activity was raised (17·1 KA units; normal 3-13) and there was evidence of increased bone resorption (hydroxyproline:creatinine ratio 0·056). Radiocalcium absorption was normal (0·66 fraction of dose/hour) with normal plasma 1,25-dihydroxy vitamin D concentration (146·7 pmol/l (58·7 pg/ml)). Plasma 25-hydroxy vitamin D concentration was high (270 nmol/l (108 ng/ml)) and plasma parathyroid hormone concentration normal (251 pg/ml). She had cortical and trabecular osteoporosis (metacarpal cortical area:total area 0·56; iliac crest bone volume 7%). There was biochemical evidence of thyrotoxicosis, with raised thyroxine concentration (167 nmol/l (13·0 μg/100 ml)); triiodothyronine concentration (4·0 nmol/l (2·6 ng/ml); and free thyroxine index (3·5). She was treated with carbimazole and was biochemically euthyroid after 40 days. Plasma calcium concentration decreased but was still above normal after 500 days' treatment (figure). By then the hydroxyproline:creatinine ratio was normal but radiocalcium absorption had increased (1·29 fraction of dose/hour) and plasma parathyroid hormone concentration had risen above the normal range to 590 pg/ml.

Comment

Both patients presented with fracture of the femoral neck and, though having no clinical features of thyrotoxicosis, were found to have biochemical evidence of the disease. Both had cortical and trabecular osteoporosis and evidence of increased bone resorption with a high fasting urinary hydroxyproline:creatinine ratio. On treatment with carbimazole this ratio returned to normal long after the patient had become biochemically euthyroid, suggesting that the effect of excess thyroid hormone on bone is prolonged.

Increased bone resorption in thyrotoxicosis causes a tendency towards hypercalcaemia,[3] leading to suppression of production of parathyroid hormone, low plasma 1,25-dihydroxy vitamin D concentrations, and malabsorption of calcium.[4] The first patient was normocalcaemic and had malabsorption of calcium and a low plasma 1,25-dihydroxy vitamin D concentration, though the plasma parathyroid hormone concentration was normal. The second patient was hypercalcaemic; had a high plasma 25-hydroxy vitamin D concentration, reflecting previous treatment with vitamin D; and had normal calcium absorption and plasma 1,25-dihydroxy vitamin D and parathyroid hormone concentrations. After treatment with carbimazole mild hypercalcaemia persisted, calcium absorption increased, and the plasma parathyroid hormone concentration became raised, suggesting coincidental hyperparathyroidism, which is associated with thyrotoxicosis[5] and may have contributed to the bone loss in this patient.

These two cases show that even in the absence of the usual clinical features of thyrotoxicosis this diagnosis should be considered in patients with fracture of the femoral neck.



Effect of carbimazole on plasma calcium concentration and fasting urine hydroxyproline:creatinine ratio in two women with thyrotoxicosis (○ = case 1, ● = case 2). Carbimazole was continued throughout the period of observation in a dose that maintained the patient in a biochemically euthyroid state.

Conversion: SI to traditional units—Calcium: 1 mmol/l≃4 mg/100 ml.

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